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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/456,429	12/08/1999	YU-HUA JI	P-015-RPI	6458

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EXAMINER:
BAKER, MAURIE GARCIA

ART UNIT	PAPER NUMBER
1627	

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Please find below and/or attached an Office communication concerning this application or proceeding.

FIC WP

Office Action Summary	Application No. 09/456,429	Applicant(s) JL et al
	Examiner Mauri Garcia Baker, Ph. D.	Art Unit 1627
<p>– The MAILING DATE of this communication appears on the cover sheet with the corresponding address –</p> <p>Period for Reply</p> <p>A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE THREE MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.</p> <p>- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.</p> <p>- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.</p> <p>- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.</p> <p>- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).</p> <p>- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).</p>		
<p>Status</p> <p>1) <input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>May 9, 2002</u></p> <p>2a) <input type="checkbox"/> This action is FINAL. 2b) <input checked="" type="checkbox"/> This action is non-final.</p> <p>3) <input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> 1035 C.D. 11; 453 O.G. 213.</p>		
<p>Disposition of Claims</p> <p>4) <input checked="" type="checkbox"/> Claim(s) <u>74-83</u> is/are pending in the application.</p> <p>4a) Of the above, claim(s) <u>75-77 and 79</u> is/are withdrawn from consideration.</p> <p>5) <input type="checkbox"/> Claim(s) _____ is/are allowed.</p> <p>6) <input checked="" type="checkbox"/> Claim(s) <u>74, 78, and 80-83</u> is/are rejected.</p> <p>7) <input type="checkbox"/> Claim(s) _____ is/are objected to.</p> <p>8) <input type="checkbox"/> Claims _____ are subject to restriction and/or election requirement.</p>		
<p>Application Papers</p> <p>9) <input type="checkbox"/> The specification is objected to by the Examiner.</p> <p>10) <input type="checkbox"/> The drawing(s) filed on _____ is/are a) <input type="checkbox"/> accepted or b) <input type="checkbox"/> objected to by the Examiner.</p> <p style="margin-left: 20px;">Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).</p> <p>11) <input type="checkbox"/> The proposed drawing correction filed on _____ is: a) <input type="checkbox"/> approved b) <input type="checkbox"/> disapproved by the Examiner.</p> <p style="margin-left: 20px;">If approved, corrected drawings are required in reply to this Office action.</p> <p>12) <input type="checkbox"/> The oath or declaration is objected to by the Examiner.</p>		
<p>Priority under 35 U.S.C. §§ 119 and 120</p> <p>13) <input type="checkbox"/> Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).</p> <p>a) <input type="checkbox"/> All b) <input type="checkbox"/> Some* c) <input type="checkbox"/> None of:</p> <ol style="list-style-type: none">1. <input type="checkbox"/> Certified copies of the priority documents have been received.2. <input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____.3. <input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). <p>*See the attached detailed Office action for a list of the certified copies not received.</p>		
<p>14) <input checked="" type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).</p> <p>a) <input type="checkbox"/> The translation of the foreign language provisional application has been received.</p> <p>15) <input checked="" type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.</p>		
<p>Attachment(s)</p> <p>1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)</p> <p>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)</p> <p>3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____</p> <p>4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____</p> <p>5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)</p> <p>6) <input type="checkbox"/> Other: _____</p>		

DETAILED ACTION

Continued Prosecution Application

1. The request filed on May 9, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/456,429 is acceptable and a CPA has been established. An action on the CPA follows.

2. Applicant's Preliminary Amendment also filed on May 9, 2002 (Paper No. 19) has been entered. Claims 52-54, 56, 58-63, 65 and 67-73 were cancelled and claims 74-83 were added. Thus, currently, claims 74-83 are pending.

Election/Restriction

3. In Paper No. 7, Group I drawn to multibinding compounds and pharmaceutical compositions comprising the compounds (original claims 1-15) was elected with traverse. A species of ligand (diltiazem) and specific multibinding compound (compound 79 in Figure 10) were also elected with traverse. The claims have been substantively amended since this election.

4. The elected species discussed above corresponds to formulas (iv) and (vi) of the now amended claims. Newly added claims 75-77 and 79 do not read on the elected species.

5. Thus, since there is currently no allowable generic claim, claims 75-77 and 79 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to non-elected species. See paragraph 6 below, section highlighted in **bold**.

6. With respect to the species election see MPEP § 803.02 (emphasis added):

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and **claims to the nonelected species held withdrawn from further consideration**. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

7. Therefore, claims 74, 78 and 80-83 are currently under examination.

Withdrawn Rejections

8. The rejection under 35 USC 102 over Gluchowski is withdrawn in view of applicant's newly filed claims that omit homodimers of ligands of formula (iii).

9. Also, the indicated allowability of previous claims 59, 60, 68 and 69 (which are related to the instant claims 78, 80 and 82) is withdrawn in view of the newly discovered reference(s) to Pifferi et al. Rejections based on the newly cited reference(s) follow. Also note new obviousness-type double patenting rejection over U.S. Patent No. 6,420,560.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 81 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 81 is indefinite because it uses the conjunction “and” in the phrase “one or both L are ligands of formulae (i), (ii), (iv) **and** (vi)” (emphasis added).

See MPEP 2173.05(h): Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. The above recitation is confusing and thus renders the claim indefinite. It is suggested to change the “*and*” to “*or*”.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the

various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 74, 78 and 80-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pifferi et al (US 5,120,730).

Pifferi et al teach dimeric benzothiazepines, see Abstract and patented claims. The benzothiazepines made by Pifferi et al have “structures related to diltiazem”, which is a known calcium antagonist (see column 1, lines 6-28, especially lines 11-14 & 21-24). This is also applicant’s elected species of ligand. The dimeric benzothiazepines of Pifferi et al are linked by a linker moiety denoted X, which can be, for example, -CH=CH-, -(CH₂)₂- or p-C₆H₄ (see patented claim 2). This reads on the instant linker when m=0, all but one Z is a bond and the remaining Z moiety is alkylene, alkenylene or arylene. Furthermore, the reference specifically teaches the linker of claim 82, see column 1, lines 54-63. Pifferi et al teaches making pharmaceutical compositions of their compounds, see column 2, lines 50-56 and patented claim 7. The reference also teaches that their dimeric compounds “display a selective [pharmacological] activity” that differs from that of diltiazem; notably, turning out to be “free of

negative ... effects characteristic of diltiazem" (see, for example, column 5, lines 30-40).

The compounds of the reference read on those of the claims when the ligands are of formula (iv) or (vi). Pifferi et al differs from the instant claims in the linkage site for the two benzothiazepine ligands.

However, the instant claims (specifically claim 82) show the linkage of benzothiazepines through an oxygen, which is also the site for linkage used by Pifferi et al (albeit a different oxygen). The instant specification also shows the linkage of benzothiazepines through the same site as Pifferi et al (see linkage site shown on the benzothiazepine structure on page 49 and specifically compound denoted (45) in Figure 10 of the instant specification).

Most importantly, the compounds of Pifferi et al and of the claims are *positional isomers* of each other. Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH₂- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). Thus, the compounds of the references and of the claims have very close structural similarities and similar utilities (see MPEP § 2144.09 "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed

compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991)).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention make the instantly claimed dimeric compounds (and pharmaceutical compositions thereof) based on the teachings of Pifferi et al of compounds having very close structural similarities and similar utilities (i.e. position isomers of the claimed compounds). One would have been motivated to do so because position isomers often have similar properties and therefore one of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (i.e. to create more efficacious compounds for treatment). One of ordinary skill would be specifically motivated to do the above as the dimeric compounds of Pifferi et al have improved pharmacological properties over the monomeric compounds (see, for example, column 5, lines 30-40).

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d

1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

16. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 74 and 83 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 10 and 11 of U.S. Patent No. 6,420,560. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. Note that claims 1-3 of the patent

recite a Markush group of ligands (formula (a)) that overlaps with the Markush group of ligands (formula (v)) in the instant claim 74. Specifically, the compounds of the patent read on the compound of claim 74 when both L are formula (v), with the difference being the compounds of the patent claims have chloro substituents and the compound of the application has fluoro substituents. However, in the generic claims of the patent, the substituents at this position are listed as halo (claim 1) or specifically, chloro or fluoro (claim 3).

The compounds of the application and of the patent have very close structural similarities and similar utilities (see MPEP § 2144.09 “An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.” *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991)). Additionally, the species of compounds in claims 74 and 83 discussed above can be “at once envisaged” from the chemical formula disclosed by claims 1-3 and 11 of the patent as the classes of substituents for phenyl group substitution are sufficiently limited and well delineated (i.e. patented claim 3 defines halo as chloro or fluoro). See MPEP 2131.02. Thus, the claims of the application would be obvious in view of the claims of the patent.

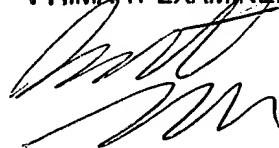
Status of Claims/Conclusion

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

20. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (703) 308-4537. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BENNETT CELSA
PRIMARY EXAMINER



Maurie Garcia Baker, Ph.D.
July 22, 2002